

61 amino acids at a position corresponding to the at least one structural part or the at least one amino acid from c);

- e) expressing the modified nucleic acid in a host cell to produce the variant alpha-amylase.--
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### REMARKS

Initially, Applicants and their representatives would like to thank Examiners Slobodyansky and Nashed for the courtesies extended during the personal interview held on February 14, 2001.

Claims 71 and 76-78 have been canceled without prejudice or disclaimer. Claims 79 and 80 have been added and therefore are pending in the present application. Claims 79 and 80 are supported by the specification and claims as originally filed. In particular, the translation step of claim 80 (step d) is described, for example, in the specification at page 12, lns. 7-16. It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

#### **I. The Written Description Rejection of Claims 76-78**

Claims 76-78 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed. In particular, the Examiner alleges that although Applicants describe a structure having the atomic coordinates depicted in Appendix 1, the specification does not provide any disclosure for coordinates for amylases other than SEQ ID NO. 13, and therefore the Examiner concludes that the specification does not contain a written description sufficient to put one skilled in the art in possession of all of the species within the claimed genus of three-dimensional structures of alpha-amylases. The rejection is respectfully traversed.

Prior to the present invention, the three-dimensional structure of only a few alpha-amylases were known. The three-dimensional structure of the Termamyl-like bacterial alpha-amylase, however, was not known or had not been accurately and/or fully predicted based on known amylase structures (such as, based on predictions made from non-Termamyl-like bacterial alpha-amylases). The present inventors have now determined the three-dimensional structure of the Termamyl-like bacterial alpha-amylase. Surprisingly, the three-dimensional

structure of the Termamyl-like alpha-amylases has been found to have, among other unique features, a special domain structure in loop 3 of the A domain, called the B domain, which structure was previously unknown and not suggested in the art. The atomic coordinates for the three-dimensional structure for SEQ ID NO. 13 as depicted in Appendix 1 are proposed by Applicants to be representative of all Termamyl-like alpha-amylases (*see* the specification at page 11, Ins. 20-22), and, thus, in addition to the three-dimensional structure for SEQ ID. NO. 13 depicted in Appendix 1, Applicants have also described (and had possession of), as discussed below, the three-dimensional of other highly homologous alpha-amylases, such as the three-dimensional structure for SEQ ID. NOS. 2, 4 and 6 (*see* the specification at page 11, Ins. 9-30; *see also* Example 1).

The Examiner alleges that Applicants have not provided any disclosure for coordinates for amylases other than SEQ ID NO:13, and therefore the Examiner concludes that the specification does not contain a written description sufficient to put one skilled in the art in possession of all of the species within the claimed genus. It is respectfully submitted that the Examiner's conclusion is not correct. Indeed, the atomic coordinates for the vast majority of the amino acids comprising the amino acid sequence of the enzyme species falling in the claimed genus are virtually identical to the amino acid coordinates for SEQ ID. NO. 13, as depicted in Appendix 1. Moreover, due to the high homology required by the claims, the remaining amino acid coordinates that are not virtually identical, are readily predicted by an artisan using the methods described in the specification and/or methods well-known in the art. Such prediction for amino acids sequences having highly homology is routine practice in the art, and is done, for example, by aligning homologous sequences and using homology based modeling programs known in the art. For example, such homology building was done by Applicants for *B. licheniformis* alpha-amylase, as described in Example 1 of the Specification.

Therefore, it is respectfully submitted that the Examiner's contention that the coordinates for any alpha-amylase other than SEQ ID NO:13 have not been described in accordance with the requirements of Section 112, first paragraph, is not correct. Thus, Applicants submit that the written description requirement is met for the claimed invention and respectfully request reconsideration and withdrawal of the rejection.

## II. The Enablement Rejection of the Claims 76-78 under 35 U.S.C. 112

Claims 76-78 stand rejected under 35 U.S.C. 112 as non-enabled. In particular, the Examiner alleges that although the specification is enabling for a method of using a three-dimensional structure having coordinates depicted in Appendix 1, that the specification does not reasonably provided enablement for a method of using "any three-dimensional structure." The Examiner further alleges that in order to practice the claimed invention, one skilled in the art would need an X-ray crystallographic three-dimensional structure of an unspecified alpha-amylase. This rejection is respectfully traversed.

An X-ray crystallographic three-dimensional structure for each alpha-amylase species falling within the claimed invention (*i.e.*, determined by crystallizing each alpha-amylase) is plainly not required to practice the claimed invention. An artisan can readily provide an accurate three-dimensional structure of an enzyme once information about the three-dimensional structure of an enzyme with sufficient homology is known, for example, by alignment between the amino acid sequences of the enzymes of interest and/or by using various computer homology based modeling programs, as exemplified in Example 1 of the Specification. In this regard, Applicants have provided the first three-dimensional structure for a Termamyl-like alpha-amylase (Appendix 1), and have provided the scope for which this three-dimensional structure is applicable, namely, enzymes with sufficiently high homology ("at least 70%") to SEQ ID NO. 13, such as SEQ ID. NOS. 2, 4 and 6. Applicants have also provided a specific example in which a three-dimensional model of an alpha-amylase which was not SEQ. ID. NO. 13 was provided. *See, e.g.*, Example 1 for *B. licheniformis* alpha-amylase.

Moreover, the claims are not, as the Examiner alleges, directed to providing "any three-dimensional structure," but rather are limited to providing a three-dimensional of an alpha-amylase for an alpha-amylase having the atomic coordinates corresponding to the atomic coordinates for SEQ ID NO. 13 as depicted in Appendix 1. It is clearly within the skill of an artisan, as exemplified in Example 1 of the specification, to provide such a three-dimensional structure for an amino acid sequence which is at least 70% homologous to SEQ ID NO.13. Indeed, as previously discussed, the atomic coordinates for the vast majority of the amino acids comprising the amino acid sequence of the enzyme species falling in the claimed genus are virtually identical to the amino acid coordinates for SEQ ID. NO:13, as depicted in Appendix 1, and, due to the high homology required by the claims, the remaining amino acid coordinates that are not virtually identical, are readily predicted by an artisan using the

methods described in the specification and/or methods well-known in the art. Thus, Applicants have clearly met the enablement requirement of Section 112.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.


### **III. The Indefiniteness Rejection of Claims 71 and 76-78**

Claims 71 and 76-78 have been rejected under 35 U.S.C. 112 as indefinite for various reasons. It is respectfully submitted that the new claims render moot the indefiniteness rejections. Applicants respectfully request reconsideration and withdrawal of the rejection.

### **IV. Conclusion**

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Date: February 28, 2001

  
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Jason I. Garbell, Reg. No. 44,116  
Novozymes North America, Inc.  
405 Lexington Avenue, Suite 6400  
New York, NY 10174-6401  
(212) 867-0123